

MAR 17 2005

## PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : MARANAS, et al.  
 SERIAL NO : 10/043,440  
 FILED : January 10, 2002  
 TITLE : METHOD AND SYSTEM FOR MODELING CELLULAR  
           METABOLISM

Grp./A.U. : 1631  
 Examiner : MORAN, Marjorie A.  
 Conf. No. : 1336  
 Docket No. : P05468US01

DECLARATION OF CHRISTOPHE H. SCHILLING  
 TO OVERCOME PRIOR ART REJECTION

I, Christophe H. Schilling being sworn, hereby declares and state the following:

1. I, Christophe H. Schilling, am Chief Scientific Officer of Genomatica, Inc.
2. I hold a Doctorial Degree in Bioengineering from the University of California, San Diego, and a B.S. Degree in Biomedical Engineering from Duke University.
3. I have reviewed the above-identified patent application, including the pending claims, the Office Action of December 16, 2004, and the references cited by the Examiner.
4. I am the author of one of the references cited by the Examiner, namely "The Underlying Pathway Structure of Biochemical Reaction Networks", *Proc. Natl. Acad. Sci. USA*, Vol. 95, pp. 4193-4198, April 1998.
5. I am also familiar with the article "Metabolic Flux Balance Analysis and the In Silico Analysis of Escherichia Coli K-12 Gene Deletions", Jeremy S. Edwards and Bernhard O. Palsson,

BMC Bioinformatics (2000) 1:1. In fact, while at the University of California, San Diego, I worked under the supervision of Professor Paulsson, and we founded Genomatica, Inc. together.

6. I consider myself to be one of at least ordinary skill in the art related to the above-identified invention.

7. I have significant disagreement with the interpretations of the Edwards and Schilling references, articulated in the Office Action of December 16, 2004.

8. One instance of such a disagreement is that the Office Action indicates that Schilling inherently teaches applying logic constraints to a flux balance analysis. This is incorrect. Neither Schilling nor Edwards discloses applying logic constraints to a flux balance analysis model.

9. The Office Action of December 16, 2004 also appears to indicate that Schilling discloses use of mixed-integer linear programming. This is also incorrect as neither Schilling nor Edwards discloses using mixed-integer linear programming.

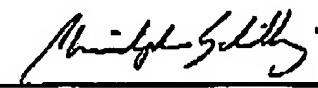
10. In Schilling, I teach linear programming, however, linear programming is fundamentally different from mixed-integer linear programming despite the similarity in name. In particular, linear programming is used to find a solution based upon particular linear constraints and an objective function. Mixed-integer linear programming allows for the introduction of discrete-binary constraints that enable fundamentally different questions to be solved with this method versus linear programming. By using this novel approach one could setup a constraint that for instance only allows a reaction to be "on" while another reaction is "off". This is not something that could in any way be accomplished with linear programming methods. Thus, linear programming problems and mixed-integer linear programming problems are fundamentally different in nature and as applied in the issue at hand, relate to fundamentally different approaches in modeling.

11. In Schilling, I represent reaction balance equations in matrix notation to provide a stoichiometric matrix, S. The equation  $S \cdot v = 0$  can be solved given a suitable objective function through use of linear programming. Such a linear programming problem is not a mixed-integer linear programming problem. Moreover, the difference between linear programming and mixed-integer linear programming is not just a difference in how a problem it is solved, it indicates a fundamental difference in the problem itself.

12. It is my opinion, contrary to the views expressed with respect to the Office Action of December 16, 2004, that none of the pending claims which accompany the response filed with this Declaration are obvious based on a combination of the Schilling and Edwards references.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Date 3/17/05

  
Christophe E. Schilling